Approach to Anemia

Introduction

Anemia literally means "without blood" (an-emia), but is used to communicate a reduced hemoglobin. The oxygen-carrying capacity of the blood is based on the number of red blood cells and how full of hemoglobin each one is. The lab we measure is hemoglobin. Low hemoglobin means low oxygen-carrying capacity of the blood. But it isn't always so simple.

Hemoglobin is measured as a concentration, as g/dL. This means that the hemoglobin is not always a perfect marker for how much hemoglobin is in the body, for the total red blood cell mass, or for the complete oxygen-carrying capacity of the blood. In most cases, it is more than adequate. In some specific cases, you can be deceived. For example, in pregnancy, both hemoglobin and plasma volume increase, but the plasma volume increases more. The hemoglobin value shows a reduced hemoglobin as the g of hemoglobin increasing less than the volume per deciliter. And yet, a woman can lose a liter of blood during delivery and then be snapping selfies while holding her baby. That same woman, not pregnant, if she suffers a gunshot wound and loses a liter of blood? She's dead in the field. Another setting where you may be deceived is in the setting of acute hemorrhage. The blood bleeding through that hole is a combination of both red blood cells and plasma. If you take a sample of a person's blood minutes after a massive GI bleed starts, the value may be falsely reassuringly normal. Give two liters of fluid, or wait for fluid shifts to balance out the changes of blood loss, and the true anemia will be revealed. You will hear this again in the clinical years and in the intern content. Giving fluid cannot induce an anemia, but it can reveal an anemia missed by the initial hemoglobin.

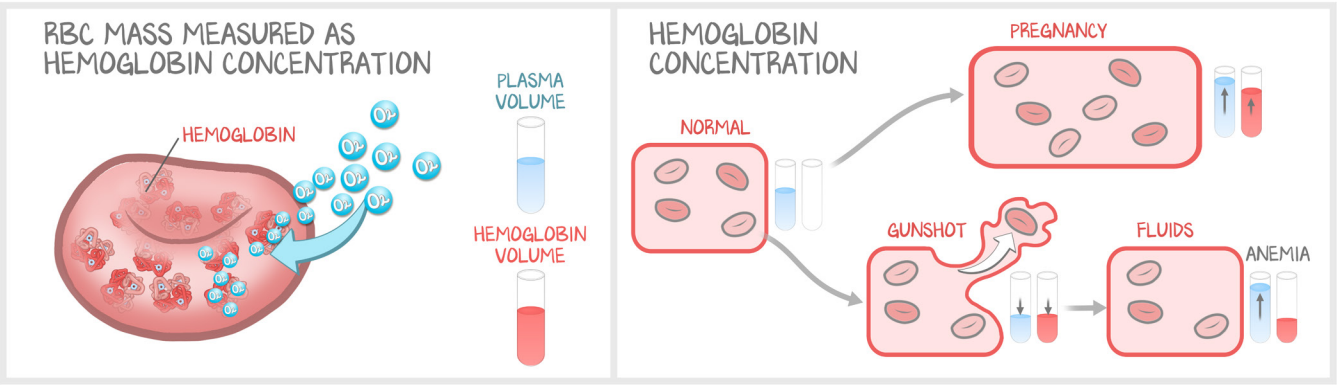

Figure 4.1: Anemia
(a) Hemoglobin is a concentration, an amount of protein in a volume. Blood is plasma and RBCs, RBCs are effectively hemoglobin. The concentration of blood can be altered by removing the red blood cells or by adding volume. (b) Pregnancy and acute blood loss are states where the hemoglobin concentration may not give an accurate assessment of the true hemoglobin capacity of the body.

The good news is that for a student of the basic sciences, except for those very specific situations (pregnancy and acute hemorrhage are the ones to know about), hemoglobin is an excellent surrogate for the blood's ability to carry oxygen. We've used the concentration of hemoglobin as the representative measurement of choice. There are hemoglobin people and there are hematocrit people. Both measure the same thing different ways. **Hemoglobin** is a concentration, measured as g/dL. **Hematocrit** is performed by spinning down a sample of blood. The heavier red blood cells sink to the bottom of the tube, leaving the plasma separated on top. The hematocrit is reported as a percentage, the percentage of the tube that is red blood cells. And while there are crit people and hemoglobin people, there really is no right way. Both are impacted by the same limitations (fluid shifts and plasma volume), and both give the same

information. In fact, while not a calculation you can rely on exactly, the hemoglobin, in g/dL is about one-third the hematocrit, in percentage. Normal hemoglobin is 14 g/dL; a normal crit is 42%. We are hemoglobin people. Dr. Williams doesn't even write the hematocrit on his sticks' shorthand in clinical practice. This lesson assumes you have the content in Hematology Oncology: General #1–#3 mastered already. We will not review the details of all the labs provided in a complete blood count—only the three values we need to start our anemia evaluation off right: hemoglobin, MCV, and reticulocytes.

A normal hemoglobin is 14–16 g/dL. The definition of anemia is below a standardized cutoff. For men, who should not ever bleed, anemia is defined as a hemoglobin < 13.5 g/dL. For women, who bleed monthly with menses, anemia is defined as a hemoglobin < 12 g/dL. But here's the thing . . . any low blood count above 10 g/dL will be asymptomatic, and, if stable (not changing), need not be investigated. This may not be the case on Step 1, but it certainly is in life. On the test, if ever you are given a value outside of the range of the TEST's reference values, consider it abnormal and meaningful for the vignette. In life, Hgb > 12 isn't even noticed, and a Hgb > 10 isn't investigated.

The symptoms of anemia reflect the severity of anemia, not the etiology. All anemia presents the same way—poor perfusion to tissues. In anemia, the volume of blood (both plasma and red blood cells) is good, but the oxygen-carrying capacity of the blood is poor. How well blood perfuses tissues has to do with the delivery-of-oxygen equation we discussed in Pulmonary (D_LO_2 = cardiac output × hemoglobin × % saturation, where hemoglobin represents the oxygen-carrying capacity of the blood). The oxygen-carrying capacity of the blood itself can be impaired if there are two few or too small red blood cells, or if the amount of hemoglobin per red blood cell falls. But the symptoms do not provide clues as to **why** they are fewer, smaller, or less packed with hemoglobin, only that there **might be** too few, too small, or less-packed-with-hemoglobin red blood cells. There are absolutely syndromes that include anemia (such as Plummer-Vinson or pernicious anemia) and there are absolutely lab tests you will get to separate the anemias (the entire subject matter of the next lesson), but the etiology of anemia is **determined by labs and not by symptoms**.

The symptoms of anemia depend on what organ is not being perfused. In general, the first noticeable symptoms in an otherwise healthy person arise around a hemoglobin of 10 g/dL. Around a hemoglobin of 8 or 9, fatigue and malaise predominate. Think of an athlete who could play an entire game at 14 g/dL but now cannot finish the game at 8–9 g/dL. As the hemoglobin drops further, into the 6–7-g/dL range, real symptoms appear. At a hemoglobin **less than 8** there will be **conjunctival pallor**. The symptoms are more acute—that same athlete now cannot make it across the field. Presyncope (brain oxygen delivery compromised) and dyspnea on exertion (cardiac output attempting to compensate for the low anemia) are felt. As the hemoglobin gets even lower, **below 5 g/dL**, life is unlikely to be sustained. If not corrected, the healthy patient will suffer from **high-output heart failure**, the system being so reliant on cardiac output to deliver oxygen that eventually the heart fails. This is why we have hemoglobin in the first place—the heart cannot pump enough plasma fast enough to deliver oxygen without the increased carrying capacity of hemoglobin. Even those who have normal cardiac function may begin to exhibit evidence of organ failure—strokes, heart attacks, and rhabdomyolysis with exercise.

Human substrate matters more than the hemoglobin number. Because the delivery-of-oxygen equation provides us with physiologic dials to turn to maintain the delivery of oxygen, those with good hearts (cardiac output) and good lungs (percent saturation) can tolerate larger changes in hemoglobin. A competitive triathlete (who isn't doping) has incredible amounts of cardiopulmonary reserve, and can therefore tolerate a large reduction in hemoglobin before suffering symptoms. In comparison, the COPDer who continues to smoke after his stent fails for coronary artery disease is unlikely to tolerate even modest changes in hemoglobin.

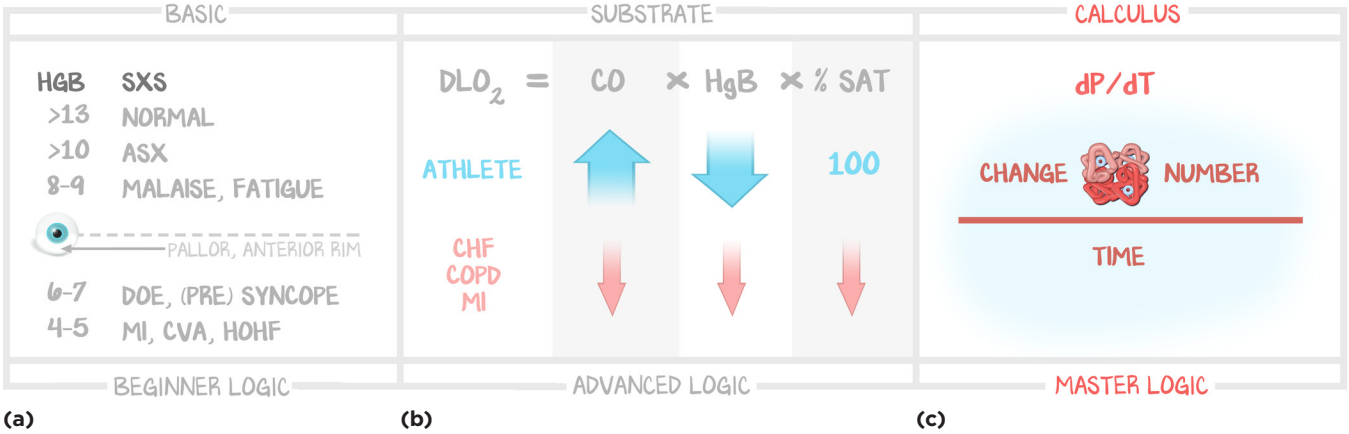

Figure 4.2: Symptoms of Anemia Relative to Substrate, Severity, and Acuity
(a) The most basic understanding is the absolute number. A lower number means less oxygen carrying capacity. Greater than 13 is normal, less than 7 and you transfuse. (b) Substrate expands that understanding to be more than just a number. Cardiovascular reserve and pulmonary disease may provoke worse symptoms at higher hemoglobin values. (c) Calculus matters most. A large change in a short time provokes more acute and severe symptoms. A relatively large change from normal that occurs over a long period of time may remain asymptomatic, despite a very low hemoglobin value.

Calculus matters most—dP/dt. Don't worry, there is no calculus. But in calculus it was all about the change in the value (dP, or in this case, dHgb) over the change in time (dT). We're talking about the change in hemoglobin over how long it took to get there. The human body is amazingly resilient, and can adjust to severe variation from the norm . . . if given enough time. Large changes in hemoglobin in a short amount of time are going to be felt in any person. But small changes in hemoglobin over a long time may go completely unnoticed. For example, normal is 14 g/dL. If a gangbanger is shot and is found to have a hemoglobin of 7 g/dL an hour later, he would be in the ICU, undergoing massive transfusion protocol, and would be unconscious. The transfusion cutoff is 7 g/dL, but losing 7 g/dL very rapidly is worse than just being at 7. A sickle cell patient with chronic hemolytic anemia lives between 7 and 8 g/dL, and is adjusted to that value of 7–8 g/dL, needs no transfusion, and, except for the constant chronic agony of sickle cell disease, generally expresses no anemic symptoms. Of course, a sickle cell patient that starts with a hemoglobin of 7 g/dL who loses 7 g/dL down to 0 g/dL has it worst of all—the lowest number, the least reserve, and an abrupt change.

The Approach to Anemia—MCV and Reticulocytes

The first steps in evaluating anemia is to combine the **mean corpuscular volume** (MCV), which measures the average size of red blood cells in the patient's sample, with the **reticulocyte index**, a marker for whether the cause is production or destruction.

All anemias are either **production** anemias (a defect of the bone marrow to produce red blood cells) or are **destruction** anemias (something else is claiming the red blood cells, and the bone marrow revs up to meet the demand of those lost). The body always wants to maintain homeostasis, and homeostasis is a hemoglobin at 14–16 g/dL. We will go into the mechanisms of how the body "knows" what concentration of hemoglobin it "wants" to be at in Proliferation #2: *Myeloproliferative Disorders*. A **reticulocyte** is a red blood cell that has been released a little too soon. Mature, fully differentiated red blood cells have no nucleus or mitochondria. A reticulocyte is a red blood cell without a nucleus but with mitochondria. Within a few days the reticulocyte will mature in the peripheral blood. But the bone marrow released the red blood cell early, because it received the signal to do so. In destruction anemias, the bone marrow can keep up with excess losses, and so will increase the production of red blood cells and increase the release of reticulocytes, called a reticulocytosis. Therefore, **a high reticulocyte**

count indicates that the **bone marrow is intact** and that the **anemia is destruction.** Conversely, a low reticulocyte count, in the presence of anemia (where there should be increased production), indicates that the bone marrow is the problem, and that it is a production anemia.

In clinical practice you will use not the reticulocyte count, but the reticulocyte index. The **reticulocyte index** is a measurement of the appropriateness of reticulocytosis based on the current hemoglobin. The lower the hemoglobin, the more you would expect reticulocytes. You will not have to calculate this number on an exam, but you will on your patients. A **reticulocyte index > 2%** indicates that the bone marrow is intact. For you, answering test questions, you will either have A LOT of reticulocytes or very few. You won't have to make close judgement calls.

RETICULOCYTE INDEX > 2%	RETICULOCYTE INDEX < 2%
Destruction anemias	Production anemia
Normocytic only	Confirmatory for microcytic and normocytic Next step for normocytic

Table 4.1: Reticulocyte Index Takeaways

Remember that this is for your fundamentals of training, the ways things ought to be, not the way things are in an academic hematologist's practice of rare presentations. If ever you find an exception to the following, call a hematologist. For the test and for clinical practice for nonhematologist subspecialists, the rest of this lesson holds true.

The **size** of red blood cells provides the main framework for the approach to anemia. **Microcytic** anemias have an MCV < 80 and are always production anemias (low reticulocyte index). **Macrocytic** anemias have an MCV > 100 and are always production anemias (low reticulocyte index). **Normocytic** anemias have an MCV between 80 and 100, and can either be destruction (high reticulocyte index) or production anemias (low reticulocyte index). By having both the MCV and reticulocyte index, you can confirm that you are in the right branch of the workup for microcytic anemia (MCV low, RI low) and macrocytic anemia (MCV high, RI low). For normocytic anemia, you use the reticulocyte index to further delineate your decision tree.

Microcytic anemias have an MCV < 80 and a reduced reticulocyte count. Microcytic anemias are evaluated with **iron studies**. Iron studies should be obtained only if the anemia you are dealing with is microcytic. The causes of microcytic anemias are **iron deficiency anemia**, **anemia of chronic inflammatory disease** (notice we inserted the "inflammatory" part), **thalassemias** (both α-thal and β-thal), and **sideroblastic anemia**. These are the subject of Anemia #5: *Microcytic Anemia*.

IRON PROBLEMS		GLOBIN PROBLEMS	
DISEASE	**NEXT LAB**	**DISEASE**	**NEXT LAB**
Iron deficiency anemia	Iron labs (low ferritin)	α-thalassemia	Hemoglobin electrophoresis
Anemia of chronic inflammatory disease	Iron labs (high ferritin)	β-thalassemia	Hemoglobin electrophoresis

Table 4.2: Microcytic Anemias at a Glance

Macrocytic anemias have an MCV > 80 and a reduced reticulocyte count. Microcytic anemias are either **megaloblastic** (impaired DNA synthesis) or nonmegabloblastic, distinguished with a blood smear. The presence of **hypersegmented neutrophils** (5 or more lobes) implies a megaloblastic anemia. The differential involves either **folate deficiency** or **B_{12} deficiency**. Those two are bolded and separated from those that follow, because obtaining B_{12} and folate levels is the appropriate reflex when faced with a megaloblastic anemia. Orotic aciduria and drugs that mess with nucleic acid synthesis are other causes of megaloblastic anemia. The absence of hypersegmented neutrophils means a nonmegaloblastic macrocytic anemia, and implies either **chronic alcohol** or **cirrhosis**. Macrocytic anemias are the subject of Anemia #6: *Macrocytic Anemia*.

MEGALOBLASTIC		NONMEGABLOBLASTIC	
Folate deficiency	Folate level, MMA	Chronic alcohol	History
B_{12} deficiency	B_{12} level, MMA	Cirrhosis	Complicated
Orotic aciduria	Yes, for Step 1		
Drugs	Methotrexate, 5-FU, 6-mercaptopurine, azathioprine, mycophenolate, hydroxyurea		

Table 4.3: Megaloblastic Anemia at a Glance

Normocytic anemias can be either **destruction** anemias (hemolysis and hemorrhage) or **production** anemias (anemia of chronic kidney disease and cancer).

Normocytic anemias that are caused by destruction of red blood cells in the presence of a normal bone marrow come down to hemolysis and hemorrhage. Hemolytic anemias demonstrate evidence of hemolysis—**LDH** is released from RBCs and elevates, **haptoglobin** binds to free hemoglobin and is undetectable, and there are **reticulocytes**. Hemorrhage can generally be spotted with the naked eye.

Normocytic anemias that are caused by production of red blood cells come down to **chronic kidney disease and cancer** (production anemias). These are also usually not difficult to spot (chronically elevated creatinine, metastatic malignancy) but can be the source of frustration on vignettes where information is deliberately held to assess your knowledge of hematology principles. Hemolytic anemias make up the vast majority of our studying in Anemia #7: *Normocytic Anemia*.

DESTRUCTION		PRODUCTION	
Hemolysis	Blood smear	Chronic kidney disease	Creatinine
Hemorrhage	Plug hole	Cancer	Various

Table 4.4: Normocytic Anemias at a Glance
Yes, the anemias are presented in the order in which Goldilocks tries the three bears' home. In subsequent lessons, we'll go into a lot more detail about the pathogenesis and evaluation of these diseases.

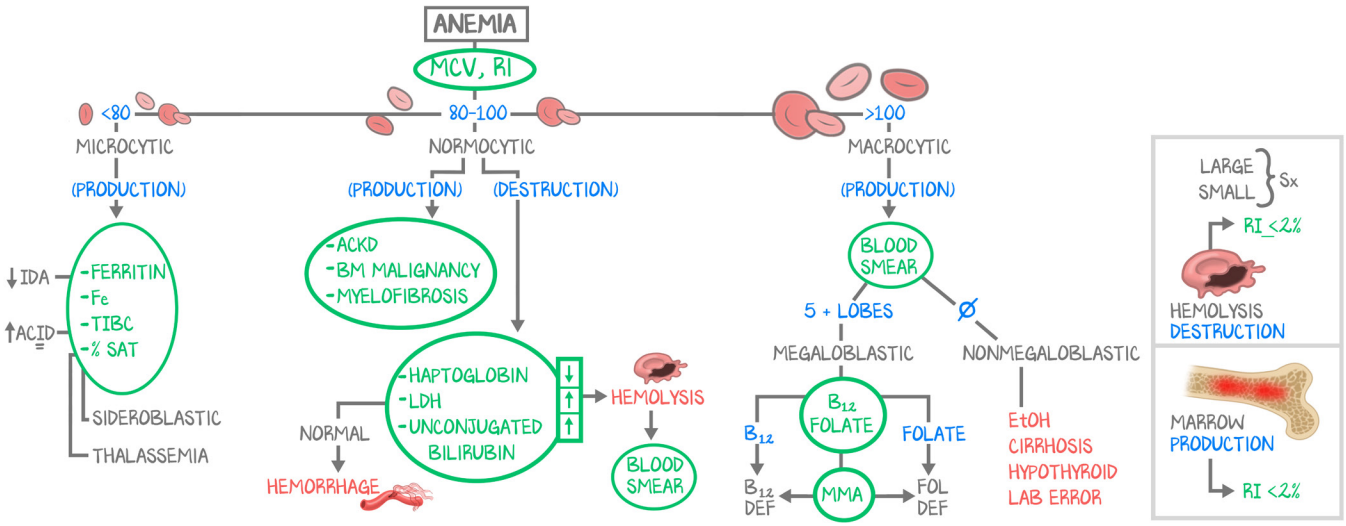

Figure 4.3: Summary of the Approach to Anemia

Using the MCV and reticulocyte count, you can narrow down the differential to three main categories—microcytic, normocytic, and macrocytic anemias. Based on the category, the most helpful next steps are listed in the algorithm, and allow you to arrive at a particular diagnosis.